Review Article

Drug Therapy

ALASTAIR J.J. WOOD, M.D., *Editor*

POSTHERPETIC NEURALGIA — PATHOGENESIS, TREATMENT, AND PREVENTION

RHONDA G. KOST, M.D.,
AND STEPHEN E. STRAUS, M.D.

SPONTANEOUS pain, pain provoked by trivial stimuli, and altered sensation accompany herpes zoster and may continue long after its characteristic rash has healed — a condition known as postherpetic neuralgia. Many approaches have been proposed to treat the pain of acute zoster, to avert progression to postherpetic neuralgia, and to alleviate postherpetic neuralgia. Few of these approaches have been proved beneficial, and postherpetic neuralgia remains a source of frustration for both patients and physicians. In this article, we summarize current knowledge of the pathogenesis of postherpetic neuralgia and developments in its treatment and prevention.

CLINICAL DISEASE

Herpes zoster typically erupts within one or two adjacent dermatomes, with thoracic, cervical, and ophthalmic involvement most common.[1-5] The lesions progress from discrete patches of erythema to grouped vesicles, which pustulate and crust in 7 to 10 days but may take a month to heal, often with anesthetic scars, changes in pigmentation, and pain.

Pain is the most common symptom of zoster,[6] often preceding the eruption by days to weeks,[5,7,8] and occasionally the only manifestation.[9] Most patients report a deep aching or burning pain, altered sensitivity to touch (paresthesia) that may be painful (dysesthesia), exaggerated responses to stimuli (hyperesthesia), or electric shock–like pains.[10-13] Pain provoked by otherwise trivial stimuli (allodynia), unbearable itching, and escalating pain in response to repeated stimulation (windup pain) are also reported.[14] These abnormal sensations resolve or persist unpredictably, making it difficult to draw absolute distinctions between pain associated with zoster and postherpetic neuralgia. Pain-induced disruption of sleep, mood, and work contributes to the impact of zoster on the quality of life, in both the short and the long term.[15]

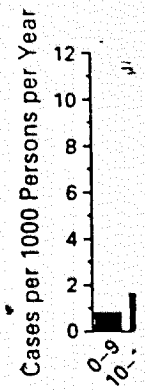
EPIDEMIOLOGY

The annual incidence of herpes zoster varies with age and immune status, from a range of 0.4 to 1.6 cases per 1000 among healthy people under the age of 20 years to 4.5 to 11 cases per 1000 among those 80 years or older (Fig. 1A).[1-4,16-18] The risk of a second attack is as high as the risk of a first attack.[2,17,19] The rate of zoster is several times higher among adults with human immunodeficiency virus (HIV) infection or cancer and 50 to 100 times higher among children with leukemia than among healthy persons of the same age.[18,20-22]

The pain of zoster tends to resolve spontaneously with time (Fig. 1B).[7,23] In the past, the pain of acute zoster was arbitrarily distinguished from postherpetic neuralgia, although the nature and timing of the symptoms often overlap. The most common definition of postherpetic neuralgia is the presence of pain more than a month after the onset of the eruption of zoster.[5,17] The condition has also been defined as pain persisting after the crusting of the skin lesions, after six weeks, or after six months.[3,24-26] Recently, the term zoster-associated pain has been used to describe all pain that occurs after the onset of the rash.[27] Nearly all patients have pain in association with acute herpes zoster, and 10 to 70 percent have postherpetic neuralgia.[2,16,28,29] Postherpetic neuralgia may develop after a pain-free interval.

The risk of postherpetic neuralgia increases with age (Fig. 1C).[1,4,5] Few children have postherpetic neuralgia,[1,18] whereas 27, 47, and 73 percent of untreated adults over 55, 60, and 70 years of age, respectively, have postherpetic neuralgia.[5,16,30] The intractability of the pain may also increase with age.[3,5,23,24] Pain lasting more than one year has been reported in 4, 22, and 48 percent of patients under 20, over 55, and over 70 years of age, respectively.[2,16] The incidence of postherpetic neuralgia is increased in patients with ophthalmic zoster and may be higher in women than in men.[1,2,16,31,32] The risk of postherpetic neuralgia is not increased in immunocompromised patients.[20,29] The actual rate among pa-

From the Medical Virology Section, Laboratory of Clinical Investigation, National Institute of Allergy and Infectious Diseases, Bethesda, Md. Address reprint requests to Dr. Kost at the Laboratory of Clinical Investigation, National Institute of Allergy and Infectious Diseases, Bldg. 10, Rm. 11N228, National Institutes of Health, 9000 Rockville Pike, Bethesda, MD 20892.



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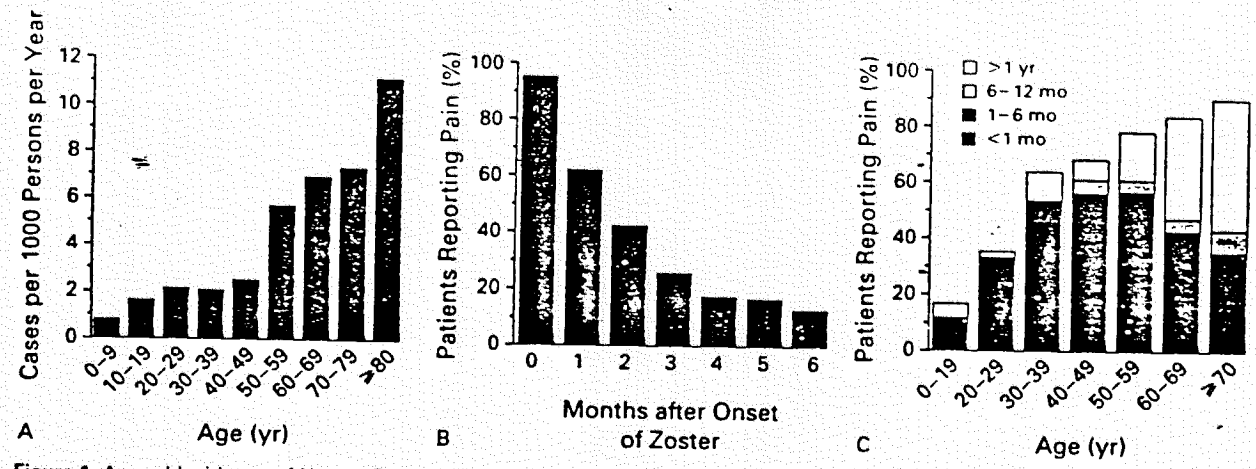

Figure 1. Annual Incidence of Herpes Zoster and Proportion of Patients with Postherpetic Neuralgia.

Panel A shows the annual incidence of herpes zoster per 1000 persons in a general medical practice.[1] Panel B shows the percentage of patients with pain persisting after the onset of the zoster-associated rash. Data are from the placebo group in one large, double-blind treatment study.[7] Panel C shows the proportion of patients with postherpetic neuralgia according to age.[16]

tients with HIV infection is difficult to determine, because such patients have high rates of recurrent and chronic zoster and often receive suppressive antiviral therapy.

PATHOGENESIS

Latency and Reactivation

Zoster is caused by the reactivation of dormant virus that was seeded in sensory nerves during an earlier bout of primary varicella.[17,33-35] Cellular immunity usually prevents the clinical re-expression of varicella–zoster virus disease by an unknown mechanism. The waning of cellular immunity to the virus with advancing age or an immunocompromised state is associated with clinical reactivation.[36,37] Infectious virus then reappears in neurons and nerve-associated satellite cells and spreads to the skin through peripheral nerves.[38]

Histopathological Features

In acute zoster, the skin is inflamed and already partially denervated, and the dorsal-root ganglion shows inflammation, hemorrhagic necrosis, and neuronal loss.[39-44] Inflammation in peripheral nerves may persist for weeks to months and usually leads to demyelination, wallerian degeneration, and sclerosis.[39,42,45] Ultimately, there may be scarring of the skin, peripheral nerves, and dorsal-root ganglia.

Pathologic changes are also evident in the central nervous system during zoster. They include acute degeneration of the dorsal horn of the spinal cord, unilateral segmental myelitis and leptomeningitis, and involvement of spinal cord segments at levels adjacent to affected skin.[39,42,44] In patients who have had zoster, atrophy of the dorsal horn has been found at autopsy in those with postherpetic neuralgia but not in those without it.[42]

PAIN

Normal sensory function is often altered in patients with postherpetic neuralgia. In one study, nearly all patients had scarred areas that were insensitive to pain, with abnormal sensation of light touch, pain, or temperature on the affected dermatome.[10] Pain is commonly precipitated by movement (mechanical allodynia) or thermal change (warm or cold allodynia). These abnormalities may extend well beyond the margins of the initial eruption (Fig. 2).[10] In another study, the degree of sensory deficit was correlated with the severity of the pain.[11] Patients with postherpetic neuralgia tend to have more sensory changes than do patients with zoster who recover without neuralgia.[11,12]

The pain associated with acute zoster and postherpetic neuralgia is neuropathic and results from injury of the peripheral nerves and altered central nervous system signal processing.[7,46] After the injury, peripheral neurons discharge spontaneously, have lower activation thresholds, and display exaggerated responses to stimuli. Axonal regrowth after the injury produces nerve sprouts that are also prone to unprovoked discharge.[47] The excessive peripheral activity is thought to lead to hyperexcitability of the dorsal horn, resulting in exaggerated central nervous system responses to all input.[47,48] These changes may be so complex that no single therapeutic approach will ameliorate all the abnormalities.

TREATMENT OF ESTABLISHED POSTHERPETIC NEURALGIA

Anecdotal reports have described the use of many agents to treat postherpetic neuralgia, ranging from B vitamins to snake venom.[16,49,50] Meaningful interpretation of data from these reports and many of the treatment and prevention trials is limited by inade-

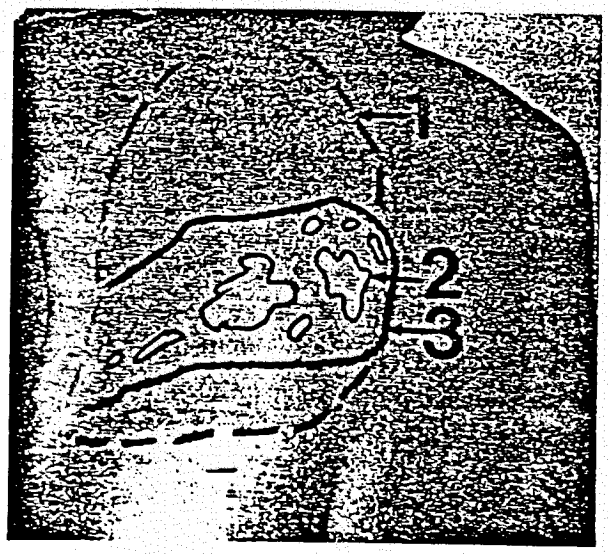

Figure 2. Sensory Disturbance in the Area of Previous Zoster. The broken line (1) indicates the margin of the area of allodynia. Areas of cutaneous scarring are shown (2). The solid line (3) indicates the margin of the area of reduced sensation to pinprick, cold, and touch. Reproduced from Watson[10] with permission of the publisher.

date descriptions of such factors as the age of the patients and the duration and severity of pain and by small samples and inadequate follow-up. Only recently have treatment studies included assessments of the severity of pain with the use of established methods, such as visual-analogue scales. Our focus is on the findings of controlled trials that evaluated pain lasting at least one month after the onset of the rash.

Analgesic and Anesthetic Drugs

Aspirin and other mild analgesic drugs are commonly used in patients with postherpetic neuralgia, but their value is limited. Ibuprofen is ineffective.[51] Neuropathic pain is generally less responsive to narcotic drugs than is nonneuropathic pain, although some patients with postherpetic neuralgia benefit from these drugs.[49,52,53]

Topical formulations of aspirin with ether, indomethacin with ether, lidocaine, and lidocaine with prilocaine have all been reported to be useful in uncontrolled trials.[13,54-56] A double-blind, controlled trial of topical lidocaine demonstrated a clear short-term benefit.[57] Anesthetic drugs such as lidocaine, ocaine, and mepivacaine are often injected locally r intravenously, because this mode of administration is reported to offer a transient benefit,[58-61] but ll these reports are anecdotal.

apsaicin

Capsaicin in high concentrations depletes substance P, a principal peptide neurotransmitter,[62] causing a burning sensation and then anesthesia. Capsaicin cream is the only drug approved by the Food and Drug Administration for the treatment of postherpetic neuralgia.[63,64] In the largest controlled trial of capsaicin, which involved 143 patients with postherpetic neuralgia of at least six months' duration, 61 percent of the patients in the capsaicin group experienced burning during application of the cream, as compared with 33 percent of the control group. After four weeks of treatment, there was a 21 percent reduction in the pain score in the capsaicin group, as compared with a 6 percent reduction in the control group ($P<0.05$).[65] Despite this finding, many investigators remain skeptical about the benefit of capsaicin, because the burning elicited during its application is intolerable for up to one third of patients and makes blinded studies impossible.

Neuroactive Agents

Tricyclic antidepressant drugs are important components of therapy for postherpetic neuralgia. Because of their ability to block the reuptake of norepinephrine and serotonin, these drugs may relieve pain by increasing the inhibition of spinal neurons involved in pain perception (Fig. 3).[67] In five trials of tricyclic antidepressant drugs for the treatment of postherpetic neuralgia, four of which evaluated amitriptyline, 47 to 67 percent of patients reported moderate-to-excellent relief of pain (Table 1).[68-72]

Amitriptyline decreases neuronal reuptake of both norepinephrine and serotonin. In one trial, desipramine, a selective inhibitor of norepinephrine reuptake, also significantly reduced pain at three and six weeks, as compared with placebo,[73] but the drug has not been compared with amitriptyline. Maprotiline, another norepinephrine-selective tricyclic antidepressant drug, was less helpful than amitriptyline in a well-designed trial.[69] Serotonin-selective drugs are of little value in the treatment of postherpetic neuralgia.[69,73] Adverse reactions to tricyclic antidepressant drugs, including confusion, urinary retention, postural hypotension, and arrhythmias, limit their usefulness in older patients, and plasma concentrations should be monitored to ensure compliance and help determine the optimal dose.

Lorazepam, a γ-aminobutyric acid agonist postulated to inhibit neurotransmission in the spinal cord and brain stem, also proved inferior to amitriptyline in a controlled trial.[70] The phenothiazine chlorprothixene is of no value,[74] but in controlled studies, other phenothiazines combined with tricyclic antidepressant drugs resulted in the partial relief of pain.[77-79]

Anticonvulsant drugs can reduce the lancinating component of neuropathic pain.[80] In an uncontrolled study, most of the patients treated with phenytoin or valproate sodium reported a reduction in shooting pains.[81] In a double-blind, controlled study, carbamazepine reduced lancinating pains but was in-

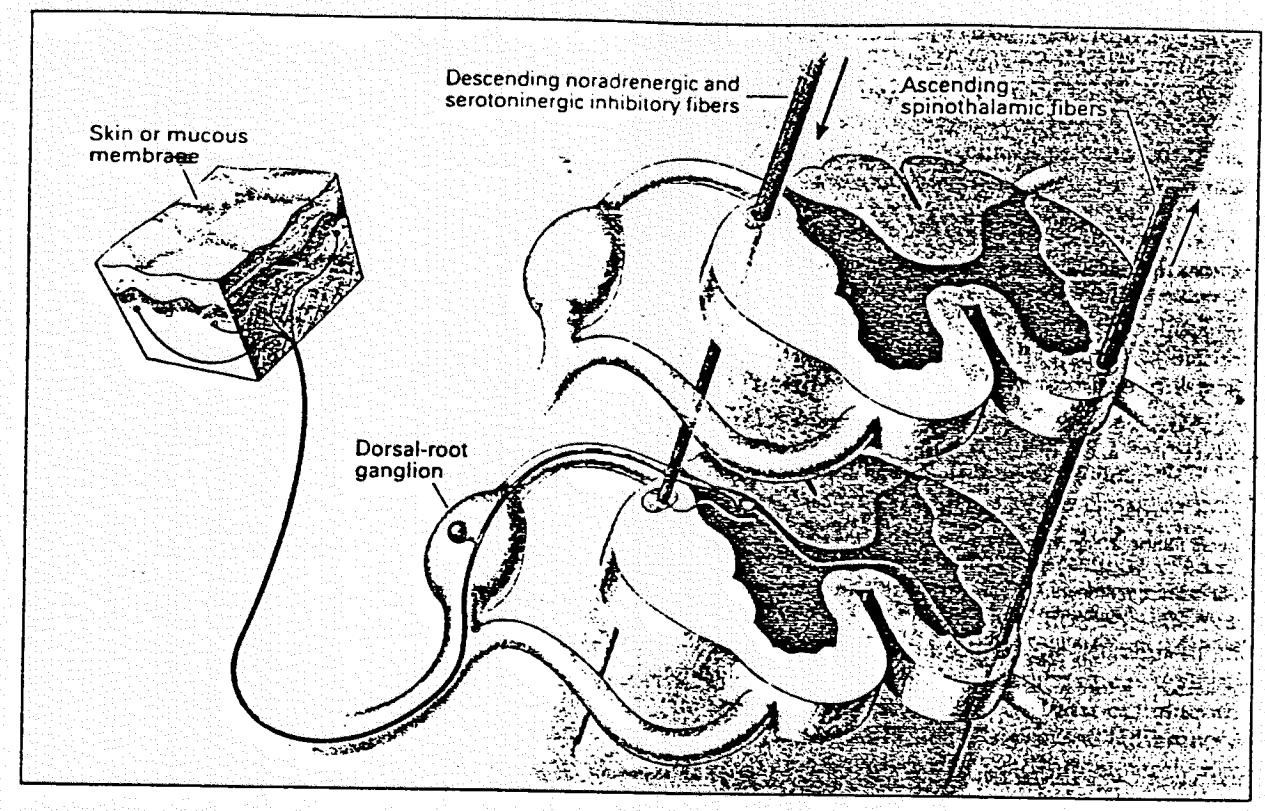

Figure 3. Pathway of Normal Pain Perception.

Noxious stimuli activate free nerve endings in the skin to generate signals that are conveyed through unmyelinated C fibers (blue) and small Aδ fibers to the neuronal bodies in the segmental dorsal-root ganglia, then proximally to the dorsal horn of the spinal cord, where they form synapses with second-order neurons.[66] Spinal cord neurons are subject to powerful descending inhibitory signals from the brain (green), mediated by the biogenic amines serotonin and norepinephrine. Drugs that potentiate the central effects of biogenic amines, such as tricyclic antidepressant drugs, may act by enhancing these descending pathways.[66] Endogenous opiates also contribute to descending inhibitory input. The net result of peripheral afferent input and descending inhibitory input is projected cephalad, joining other ascending fibers in the contralateral spinothalamic tract (orange). Information from the spinothalamic tract is integrated with input from brain-stem and cortical areas for the perception of specific aspects of pain, as well as more general affective components of pain perception.

effective for continuous pain.[75] The combination of clomipramine and carbamazepine afforded only partial relief in a controlled trial,[76] and combinations of other antidepressant and anticonvulsant drugs had some benefit in uncontrolled trials.[82]

Nonpharmacologic Interventions

Neurosurgical procedures are treatments of last resort for intractable pain. In small studies, electrical stimulation of the thalamus and anterolateral cordotomy to interrupt the spinothalamic tract have provided relief in patients with postherpetic neuralgia.[83,84] Electrocoagulation of well-defined areas of the dorsal root has been attempted, but the procedure carries a substantial risk of prolonged hemiparesis and sensory deficits, and a recent consensus conference did not advocate its use.[85,86]

A phenomenon known as "counterirritation" has been reported to relieve postherpetic neuralgia by reintroducing normal inhibition of the small fibers in the spinal cord.[86] Data from small studies suggest that ethyl chloride spray, which evaporates rapidly and causes a freezing sensation, and transcutaneous electrical nerve stimulation provide partial-to-complete relief of pain in some patients with postherpetic neuralgia.[86,87] A trial of acupuncture, as compared with mock transcutaneous nerve stimulation, revealed no benefit.[88]

Treatment Recommendations

Postherpetic neuralgia is difficult to treat, and therapy must be individualized. Elderly patients are at greatest risk for prolonged pain. Coexisting medical conditions, the risk of drug interactions, and the quality of life must be considered in designing a treatment plan for an elderly patient. It is important to introduce and modify interventions sequentially and to discard those that are ineffective or poorly tolerated. As initial therapy, we recommend topical lidocaine–prilocaine cream or 5 percent lidocaine gel.

TABLE 1. CONTROLLED TRIALS OF NEUROACTIVE DRUGS FOR THE TREATMENT OF POSTHERPETIC NEURALGIA.*

TRIAL	TREATMENT	COMPARATIVE TREATMENT	NO. OF PATIENTS	AVERAGE AGE (RANGE)	DURATION OF PAIN AT ENROLLMENT (RANGE)	PAIN ASSESSMENT	EFFECTIVE?
				yr	mo		
Watson et al.[68]	Amitriptyline, 75 mg/day	Placebo	24	66 (49–81)	>3	VAS, DES	Yes ("excellent" in 67%)
Watson and Evans[69]	Amitriptyline, 100 mg twice a day	Zimeldine (crossover)	15	62 (34–77)	>6	VAS, CAT	Yes (60% of patients receiving amitriptyline had a good response)
Max et al.[70]	Amitriptyline, 12.5–150 mg/day	Lorazepam (0.5–6.0 mg/day) or placebo	58	72 (25–86)	>3	CAT, DES	Yes (47% had a moderate or better response with amitriptyline)
Watson et al.[71]	Amitriptyline, 100 mg/day (average dose)	Maprotiline, 100 mg/day (average dose)	35	71 (55–85)	>3	VAS	Yes (66% had improvement with amitriptyline; 66% had improvement with maprotiline)
Kishore-Kumar et al.[72]	Desipramine, 12.5–250 mg/day	Benztropine	26	62 (38–79)	28.5 (3–96)	CAT	Yes (after 3 wk)
Kishore-Kumar et al.[73]	Buspirone, single 20-mg dose	m-Chlorophenylpiperazine	20 (11 with PHN)†	66 (40–80)	>2	VAS, CAT	No
Nathan[74]	Chlorprothixene, 50 mg twice a day	Placebo (crossover)	17 (13 with PHN)†	NS	NS	DES	No
Killian and Fromm[75]	Carbamazepine, 400 or 600 mg/day	Placebo	42 (6 with PHN)†	52 (36–83)	>6	DES	No
[illegible]erson et al.[76]	Clomipramine, 10–75 mg/day, and carbamazepine, 150–1000 mg/day	TENS	29 (16 in the drug group and 13 in the TENS group)	NS	>3	VAS	Yes

*VAS denotes visual-analogue scale, DES patient's or authors' description, CAT patient's assessment from a list of categories (e.g., poor, fair, good, or excellent response to treatment or no, slight, moderate, or complete relief), PHN postherpetic neuralgia, NS not specified, and TENS transcutaneous electrical nerve stimulation.

†The study included patients with pain attributed to various causes.

The efficacy of this treatment can be determined within a day or two. If even only partially effective, it may be continued while other therapies are tried. We do not recommend topical capsaicin. Nonnarcotic analgesic drugs are usually ineffective, but a brief trial may be indicated. Narcotics may also be tried, as long as the risks of sedation and dependence are recognized. If relief is incomplete with small doses of a narcotic agent, it should be withdrawn. If analgesia is ineffective, a tricyclic antidepressant drug should be tried. Amitriptyline or desipramine, which may be tolerated better than other agents in older patients, should be started at a low dose (12.5 to 25 mg) at bedtime and may be increased weekly until the pain subsides or side effects become unacceptable. Maprotiline or nortriptyline may be tried if the first drug is not effective. Patients need to be advised that there may be a delay of several weeks in achieving the maximal benefit from the antidepressant drug. If only partial relief is achieved, an anticonvulsant drug can be added. Some pain-management specialists believe that a tricyclic antidepressant drug should be tried before a narcotic drug.

Nonpharmacologic, noninvasive, and nontraditional therapies, such as transcutaneous electrical nerve stimulation, hypnosis, biofeedback, and other cognitive and behavioral techniques, complement the traditional medical treatment of postherpetic neuralgia.[89] For the patient with severe pain, referral to a pain-management specialist may be appropriate. A list of pain clinics can be obtained from the American Pain Society (telephone number, 708-966-5595). Educational materials for patients are available from the Varicella–Zoster Virus Research Foundation (telephone number, 212-472-3181), a nonprofit advocacy organization.

PREVENTION OF POSTHERPETIC NEURALGIA

The lack of predictably beneficial treatment for established postherpetic neuralgia has prompted a focus on its prevention. Careful definitions and methods are required to distinguish relief of early pain from prevention of late pain, although there is considerable overlap in the symptoms of acute zoster and postherpetic neuralgia.

Corticosteroids

Five controlled trials have evaluated the use of corticosteroids to reduce the inflammatory features of

zoster and prevent the injury that follows it. The drugs were beneficial in two of the trials and not beneficial in two others (Table 2).[25,30,90-92] The fifth trial involved 208 adults 50 years old or older with localized zoster who were given a placebo, high-dose prednisone alone, acyclovir alone, or acyclovir plus prednisone for 21 days.[92] The acute neuritis resolved significantly earlier in the prednisone group than in the other groups, with a shorter period of analgesic treatment required and an earlier resumption of normal sleeping patterns and activity. Prednisone had no effect, however, on postherpetic neuralgia.

Nerve Blocks

There are many anecdotal reports of the efficacy of infiltration of the skin, peripheral nerves, or paravertebral or epidural spaces with local anesthetic drugs in patients with zoster.[59,60,93-95] Data on the relief of acute pain, however, cannot be extrapolated to predict the prevention of postherpetic neuralgia. A large retrospective study suggested that any benefits of somatic-nerve blocks are limited to the first two months of pain,[93] a conclusion supported by the results of a small placebo-controlled study of direct sympathetic blockade[95]; in other studies, sympathetic-nerve blocks were ineffective.[58,96] Although nerve blocks are effective for the immediate, short-term relief of acute zoster pain,[49] well-designed, controlled trials of their efficacy in preventing postherpetic neuralgia have not been performed.

Antiviral Drugs

Some nucleoside analogues affect early virologic events and healing in acute zoster. The ability of any of these drugs to prevent postherpetic neuralgia is less certain, because few studies were designed to collect meaningful data about prolonged pain. Data from the largest and best-designed trials are summarized in Table 3.

Among seven double-blind, placebo-controlled trials of adequate doses of oral acyclovir in patients with zoster rash of less than 72 hours' duration (Table 3),[6,7,92,97-101] three reported a significant reduction in pain at some time after the onset of zoster, but the reduction was invariably short-lived.[6,92,100,101] The outcome was best in patients with ophthalmic zoster.[101] In one controlled study without a placebo group, treatment with acyclovir reduced the acute pain but not the postherpetic neuralgia.[102] Four of the studies showed a reduction in early pain without a lasting effect on postherpetic neuralgia.[7,92,97,100] A pooled analysis of four trials of acyclovir, as compared with placebo, revealed a 42 percent reduction in the likelihood of postherpetic neuralgia.[106]

The inconclusive results of the acyclovir trials have prompted debate on two issues: how the effects of an early intervention on postherpetic neuralgia should be ascertained, and whether postherpetic neuralgia is the proper end point. A drug trial that examines the relief of postherpetic neuralgia in the subgroup of treated patients with zoster who subsequently have neuralgia but ignores the treated patients whose pain resolved before an arbitrary point in time can result in misleading conclusions about the drug's benefit.[27] Furthermore, what probably matters most to the patient is the total discomfort, from the time of its onset until its relief — that is, the zoster-associated pain — whether acute or postherpetic.[27] Zoster-associated pain has been assessed in recent studies of new antiviral agents.

TABLE 2. PLACEBO-CONTROLLED TRIALS OF ORAL CORTICOSTEROIDS FOR THE PREVENTION OF POSTHERPETIC NEURALGIA.

TRIAL	CORTICOSTEROID TREATMENT	COMPARATIVE TREATMENT	NO. OF PATIENTS	AVERAGE AGE OR RANGE (YR)	DURATION OF RASH AT ENTRY	DEFINITION OF PAIN	EFFICACY		
							REDUCED EARLY PAIN	REDUCED PAIN AT 1 MO	EFFECT ON PHN AT LAST VISIT*
Eaglstein et al.[25]	Triamcinolone, 16 mg 3 times a day tapered over a period of 21 days	Placebo	35	21–91	"Early"	Persisting >2 mo	Yes	Yes (in patients >60 yr)	Yes at 3 yr
Keczkes and Basheer[90]	Prednisolone, 40 mg/day tapered over a period of 28 days	Carbamazepine	40	67	2–8 days	Persisting >2 mo	—	Yes	Yes at 1 yr
Clemmensen and Andersen[30]	Prednisone, 45 mg/day tapered over a period of 21 days	Corticotropin or placebo	60	56	<7 days	Persisting >6 wk	Yes	No	No at 4 mo
Esmann et al.[91]	Prednisolone, 40 mg/day tapered over a period of 21 days	Placebo	78	72	<96 hr	Zoster-associated	Yes	No	No at 26 wk
Whitley et al.[92]	Prednisone, 60 mg/day tapered over a period of 21 days	Acyclovir or placebo	208	62	<72 hr	Zoster-associated	Yes	Yes	No at 6 mo

*PHN denotes postherpetic neuralgia.

TABLE 3. CONTROLLED TRIALS OF ORAL ANTIVIRAL DRUGS FOR THE PREVENTION OF POSTHERPETIC NEURALGIA.*

TRIAL	TREATMENT	COMPARATIVE TREATMENT	NO. OF PATIENTS	AVERAGE AGE (RANGE)	DEFINITION OF PAIN	PAIN ASSESSMENT	EFFICACY	
							REDUCED EARLY PAIN (<1 MO)	EFFECT ON PHN AT LAST VISIT
				yr				
McKendrick et al.[97]	Acyclovir, 800 mg 5 times daily for 7 days	Placebo	205	72 (60–92)	All	VAS	Yes	No at 6 mo
Huff et al.,[†] Huff[98]	Acyclovir, 800 mg 5 times daily for 10 days	Placebo	187	— (55–58)	All	CAT	Yes	Yes at 1–3 mo, no at 6 mo
Wood et al.[7]	Acyclovir, 800 mg 5 times daily for 7 days	Placebo	364	72 (60–96)	All	CAT	Yes	No at 6 mo
McKendrick et al.[99]	Acyclovir, 800 mg 5 times daily for 7 days	Placebo	376	>60	Persisting >1 mo	VAS	NS	No at 6 mo
Morton and Thomson[100]	Acyclovir, 800 mg 5 times daily for 7 days	Placebo	83	52	All	VAS, CAT	Yes	Yes at 2 mo, no at 6 mo
Harding and Porter[101]	Acyclovir, 800 mg 5 times daily for 10 days	Placebo	46	62	All	VAS	No	Yes at 2–5 mo, no at 6 mo
Wood et al.[102]	Acyclovir, 800 mg 5 times daily for 7 or 21 days	With or without corticosteroid	400 (202 received acyclovir alone)	59	All	CAT, DES	No	No at 6 mo
Whitley et al.[92]	Acyclovir, 800 mg 5 times daily for 21 days	Placebo or corticosteroid	208 (135 received acyclovir alone)	61	All	NS	Yes	No at 6 mo
ing et al.[103]	Famciclovir, 500 or 750 mg 3 times daily for 7 days	Placebo	419	50	Persisting after healing	CAT	Yes	Yes at 5 mo
deGreef[104]	Famciclovir, 250, 500, or 750 mg 3 times daily for 7 days	Acyclovir, 800 mg 5 times daily for 7 days	545	— (43–54)	Zoster-associated	NS	No	No at 6 mo
ather et al.[105]	Valacyclovir, 1 g 3 times daily for 7 or 14 days	Acyclovir, 800 mg 5 times daily for 7 days	1141	68	Zoster-associated	CAT	Yes	Yes at 6 mo

*The duration of the rash at the time of enrollment was less than 72 hours in all the trials. PHN denotes postherpetic neuralgia, VAS visual-analogue scale, CAT patient's assessment from a list of categories (e.g., poor, fair, good, or excellent response to treatment or no, slight, moderate, or complete relief), DES patient's or authors' description, and NS not specified.

The nucleoside analogue famciclovir has in vitro activity against varicella–zoster virus that is similar to the activity of acyclovir, but famciclovir is more bioavailable when administered orally, and its active metabolite, penciclovir triphosphate, has a longer intracellular half-life (9.1 hours) than does acyclovir (0.8 hour). In one study, 419 otherwise healthy adults with zoster received famciclovir or placebo for seven days and were followed for five months; postherpetic neuralgia was defined as pain persisting after the healing of skin lesions. The median number of days to the disappearance of pain was significantly lower in the patients who received famciclovir than in those who received placebo (Table 3).[103] The analytic method used in this study, however, makes a comparison with the acyclovir trials difficult.[98,100,101] In a comparative trial of famciclovir and acyclovir in 545 otherwise healthy adults with zoster in which all zoster-associated pain was documented for six months, the time to the disappearance of pain was similar in the two treatment groups.[104]

Valacyclovir, a pro-drug of acyclovir, is highly bioavailable when administered orally, leading to plasma acyclovir concentrations similar to those achievable only with intravenous acyclovir. In a study of patients over the age of 50 years with mild-to-moderate pain treated with either valacyclovir for 7 or 14 days or acyclovir for 7 days, either valacyclovir regimen was more effective in relieving zoster-associated pain than acyclovir, and a smaller proportion of patients receiving valacyclovir had pain persisting for 6 months (19 percent, as compared with 26 percent of the acyclovir recipients; $P=0.02$).[105]

Combination Therapy

The early evidence that corticosteroids prevent postherpetic neuralgia (reviewed above) was not sufficiently compelling to dispel the concern that such treatment could be deleterious.[107] The availability of acyclovir provided a rational safeguard against corticosteroid-induced enhancement of viral replication. Combination therapy with a corticosteroid and an antiviral drug in patients with zoster has been evaluated in two trials. In one study, acyclovir was given for 7 or 21 days, either alone or in combination with prednisolone (40 mg daily, tapered over a period of

21 days), in patients with at least moderate pain.[102] The proportion of patients in whom acute pain was reduced was significantly larger in the group treated with prednisolone plus acyclovir than in the group treated with acyclovir alone. At six months, however, there were no differences in postherpetic neuralgia in the two groups.[102] In the study of 208 patients treated for 21 days with placebo, prednisone, acyclovir, or acyclovir plus prednisone, cited above, the patients receiving combination therapy required a shorter period of analgesic-drug therapy and had an earlier return to normal activity and uninterrupted sleep than the patients treated with either drug alone.[92] At six months, however, the proportions of patients with postherpetic neuralgia did not differ among the treatment groups.

Recommendations for Prevention

If begun within 72 hours after the appearance of the rash, famciclovir, valacyclovir, or acyclovir reduc-

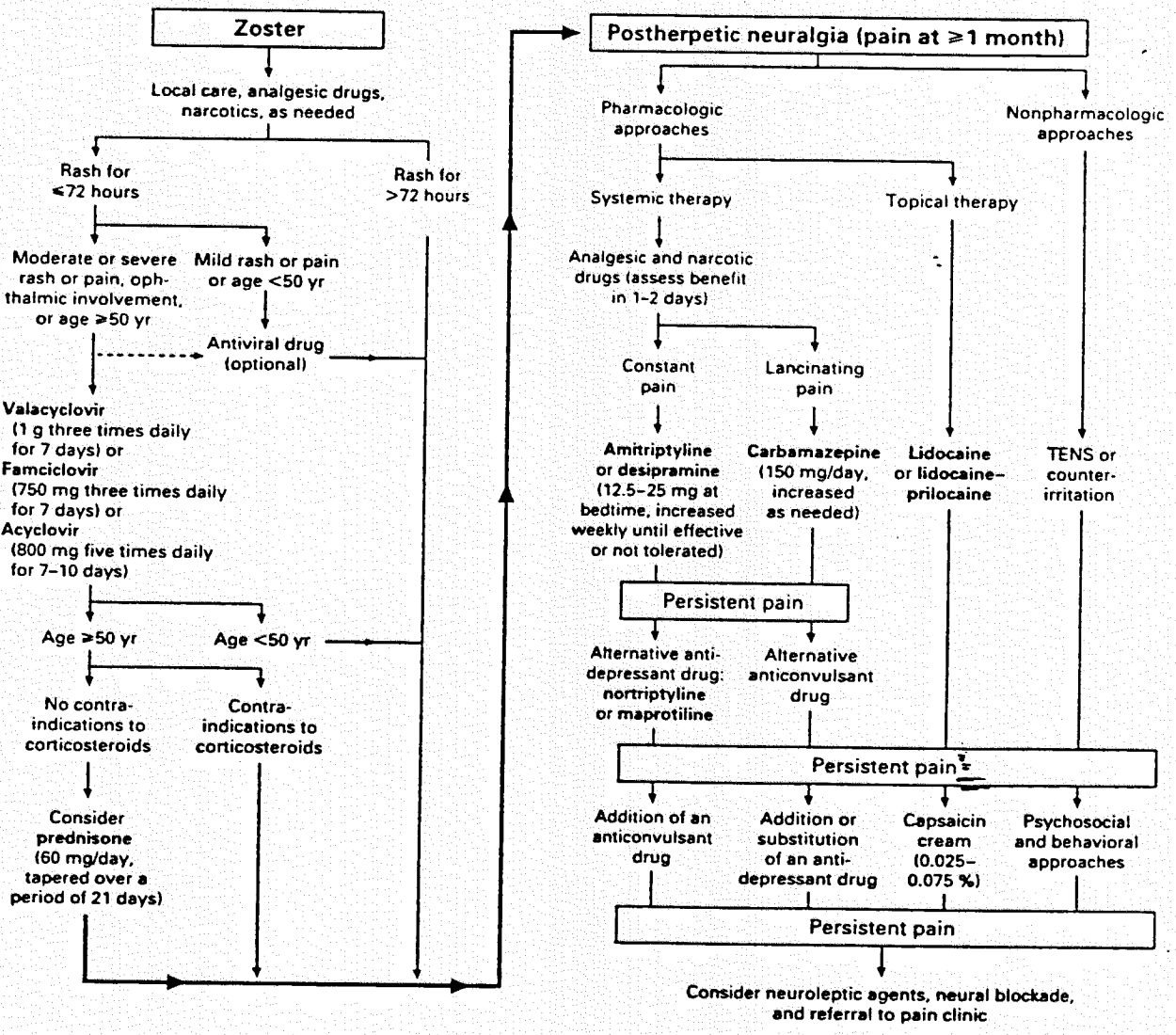

Figure 4. Approaches to the Treatment and Prevention of Acute Zoster-Associated Pain and Postherpetic Neuralgia.

Medications shown in bold have been demonstrated to be effective on the basis of fairly convincing data from controlled trials. The decision to use antiviral drugs in patients with zoster must be individualized, but the prompt use of antiviral therapy in older patients or those with ophthalmic involvement is recommended. Younger patients with mild eruptions and little pain do not require antiviral therapy. Corticosteroids should be considered in older patients if there are no contraindications (e.g., diabetes mellitus, hypertension, or glaucoma). Patients with neuropathic pain within one month after the onset of zoster may be treated early, on an empirical basis. The therapeutic approaches for established postherpetic neuralgia are more numerous than those for acute zoster-associated pain, but their value is less well documented. Primary approaches include a topical anesthetic drug and trials of analgesic and narcotic drugs, with the addition of an antidepressant drug if the former prove ineffective, inadequate, or poorly tolerated. TENS denotes transcutaneous electrical nerve stimulation.

es acute pain in immunocompetent patients with zoster,[7,92,97,98,100,103-105] thus providing relief in the greatest number of patients, irrespective of the effect on postherpetic neuralgia. Famciclovir and valacyclovir need to be given less often than acyclovir and may be slightly superior to acyclovir in shortening the duration of zoster-associated pain,[103,104] but at present, there is no reason to recommend one drug over another.

Although corticosteroids do not alter the course of postherpetic neuralgia, the demonstration that they improve the quality of life after zoster justifies their administration in combination with an antiviral drug in high-risk patients 50 years of age or older with moderate-to-severe pain in whom corticosteroids are not contraindicated.[92] Whether effective analgesia early in the course of zoster alters the evolution of postherpetic neuralgia is not known.[104] It is simply good medical practice to provide adequate around-the-clock analgesia with the use of a narcotic drug or a nerve block, if necessary. An algorithm integrating recommendations for the prevention and treatment of postherpetic neuralgia is shown in Figure 4.

FUTURE APPROACHES

Future studies of pain in patients with zoster will be most useful if they are carefully designed, with the documentation of early and late pain, structured assessment of pain and quality of life, and enrollment of patients at highest risk for postherpetic neuralgia. It is now apparent that potent antiviral drugs do not adequately prevent postherpetic neuralgia. Even treatment that combines corticosteroids with antiviral drugs has limitations. Many of the pathologic events of zoster that cause neuropathic pain and postherpetic neuralgia may have occurred by the time the rash appears.[108] The common practice of withholding therapy for postherpetic neuralgia until weeks have passed neglects an opportunity to intervene while some of the changes are still reversible. Early, expectant treatment with a low dose of a tricyclic antidepressant or anticonvulsant drug in elderly patients, who have an increased risk of postherpetic neuralgia, should be evaluated.

An emerging literature suggests that antagonists to *N*-methyl-D-aspartate receptors may lessen neuropathic pain by altering abnormal central nervous system processing. The available antagonists of these receptors, such as ketamine and dextromethorphan, reduce windup and neuropathic pain but have many adverse effects.[14]

The best way to prevent postherpetic neuralgia may be to prevent zoster itself. The live Oka-strain vaccine recently approved by the Food and Drug Administration prevents varicella. It will take decades, however, to know how durable the immune response to the vaccine is and whether the rates of subsequent exogenous reinfection or viral reactivation remain low throughout life.[21] As humoral and cellular responses to varicella–zoster virus wane with age, vaccination may reinvigorate these responses. Immunization of both adults who are immune to varicella–zoster virus and those who are not immune has yielded promising increases in humoral and cytotoxic cellular immune responses, as compared with age-related base-line levels.[109,110] These advances suggest that some day postherpetic neuralgia will be eliminated.

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